In human, fertility is compromised by several exogenous and endogenous factors. The most important exogenous cause is chronic exposure to endocrine-disrupting compounds (EDCs), which includes a wide range of pesticides. Chronic exposure to these pesticides such as, endosulfans, dieldrin, aldrin, DDT, herbicides atrazine and the fungicide vinclozolone causes reproductive toxicities that lead to infertility in both sexes, high rate of miscarriage and altered sex ratio. This review article link the relationship between fertility and long term exposure to various pesticides.

**Keywords:** Fertility, Pesticides, miscarriage

**INTRODUCTION**

Infertility is defined as the, failure to attain pregnancy after one year of unprotected sexual intercourse (Purvis and Christiansen, 1992). Several environmental endocrine-disrupting compounds (EDCs) are concern for adverse human health. Exposure to these compounds decline reproductive capability. Current facts in men proposed the incidence of secular declining trend in testosterone levels and possibly semen quality and some have imagine that this may be associated to human contact to EDCs (Travison et al., 2007; Andersson et al., 2007; Swan et al., 2000). A variety of environmental chemicals are responsible to altered hormone levels through different biological mechanism and effects including, hormone receptors, hormone synthesis, secretion or metabolism. The health impact of sub-clinical modification in circulating hormone levels remains unclear. There is a limited but mounting body of proof that environmental and professional exposure to a number of usually used chemicals is linked with hormone level alterations as a lot of persons are exposed to usually used chemicals, for example, several pesticides are responsible to enhance reproductive and other endocrine-related disease (CDC, 2005). Farmers are the focal consumer of pesticides and enormously exposed group toward pesticides by loading, mixing and applying pesticides during working in fields. A variety of agricultural pesticides are used in clouding livestock herbicides, fungicides, crop insecticides and fumigants. Crop herbicides are used mainly about 50–93%, fungicides (11–14%), crop insecticides (48–59%) and livestock insecticides (24–37%) (Mandel et al., 1996; Alavanja et al., 1996; Reynolds et al., 1998). Users may be exposed to pesticides by different ways, such as inhalation (absorption through the lungs) dermal contact...
(absorption through the skin or eyes) or ingestion (through the mouth) (Amoguis et al., 2012).

Most of the pesticides causes reproductive toxicities by interfering with the physiology of endocrine system (Cocco, 2002; Tiemann, 2008; Tiemann, 2008). Pesticides like, endosulfans, dieldrin, aldrin, DDT, herbicides atrazine and the fungicide vinclozoline are considered as endocrine disruptor chemicals (Pan, 2009). Both male and female reproductive systems are negatively affected by pesticides exposure (Kumar, 2004; Shojaei and Abdollahi, 2012). Chronic pesticides exposure causes decreased fertility in both sexes, high rate of miscarriage, altered sex ratio and has also anti-androgenic effects (Frazier, 2007). Pesticides exposure causes hormonal imbalance that eventually leads to infertility and sterility. Pesticides like, carbamates, pyrethroids, organophosphatases, Thio-and dithiocarbamates, chlorophenoxy acids and chlormethylphosphoric acids reduces testosterone concentrations in male after acute exposure during exposure season (Evamarie et al., 1999). A pesticide that changes the physiology of endocrine system by acting as hormone agonists/antagonists or changing endogenous steroid hormonal level may negatively affect the developmental, biochemical and behavioral functions that are very important for reproductive success (Gerald et al., 1997). Pesticides are endocrine disrupting chemicals (EDCs) that interfere with the synthesis, transport, metabolism and elimination of hormone there by, changing the concentration of natural hormone (Gore, 2010). Up to now a totals of 101 pesticides have listed to be endocrine disruptors (EDs) by the pesticides action network UK (PAN, 2009). In Pakistan especially in district Dir (lower) the awareness about pesticides hazardous effects is lacking in farmers either due to illiteracy or poverty. These farmers never use masks, gloves, eye glasses and other protective coverings during fumigations. They even never wash their hands after fumigation and take their breakfast or meal in their fields. During fumigation, all the clothes and body of farmers are washed by pesticides solutions. They are also addicted to sniff which during fumigation are contaminated by pesticides. For the sake of high yields with low efforts they uses excessive and multiple pesticides. These farmers are exposed to pesticides from generation to generation (GhulamN et al., 2014).

Endosulfan

Endosulfan(6,7,8,9,10-hexachloro-1,5,5a,6,9,9a -hexahydro-6,9-methano 2,4,3benzodioxathiepin-3 oxide) is a wide range insecticide. In 1954 registered for use in the United States, to manage agricultural insect and mite pests on a variety of field, and vegetable, fruit crops. Endosulfan is composed of two stereo chemical isomersα-endosulfan and β-endosulfanup to 70% and 30 % correspondingly. The records from 1987-1997 point out that an average domestic use is about 1.38 million pounds of energetic ingredient for each year (U.S. EPA, 1980). It is broadly used against a wide range of agricultural pests in India and about 81,000 metric tons of endosulfan was pretend throughout 1999–2000 (Anonymous, 2001). Oral LD50 (lethal dose enough to kill 50% of population) endosulfan in mice is 80 mg/kg and it has been classify as a practically hazardous (class II) pesticide (WHO, 2002). The chronic and sub-acute toxicity studies of endosulfan in animals show that the immune system, testes, liver and kidneys are the focal target organs (ATSDR, 2000). In current year there has been increasing disquiet concerning toxicity of a several chemical counting pesticiderson the male reproductive system (Murray et al., 2001; Sharpe, 2001). Contact of younger 3 weeks old animal, prove exhaustion of spermatid count. The sperm count was also reduces day by day by a dose of 2.5 mg/kg/day (Sinha et al., 1997). Low sperm count was also reported by the same examiner when mature mice were treated at 5 mg/kg/day (Sinha et al., 1995). The result of some recent studies have revealed that contact of pregnant mice to endosulfan at 1 mg/kg/day from day 12 during parturition leads to reduce spermatogenesis in progeny (Sinha et al., 2001). Another report showed comparable remarks at 3 mg/kg/day but not at 1.5 mg/kg/day as well as they certified this to strain disparity. Consequently experimental studies proposed that endosulfan can influence the male reproductive system, in addition the effect will be larger if contact occur throughout the developmental stage (Dalsenter et al., 2003).

Dieldrin

The broadly used insecticide dieldrin is well recognized endocrine disrupting compound. It is tremendously toxic and difficult to metabolize and weakly biodegradable. Since 1970s the compound have been broadly controlled or banned, they remain at about 8 p.p.bin human blood, adipose and other tissues (Jorgenson, 2001; Poon et al., 2005). Dieldrin has anti-androgenic property (Andersen et al., 2002) and activate extracellular regulated kinases in cells expressing estrogen receptors (ER) (Bulayeva and Watson, 2004). Dieldrin also amplify ERb expression in the company of estradiol (E2)increasing its estrogenic result (Grunfeld and Bonefeld-Jorgensen, 2004). Dieldrins excite apoptosis by inducing mitochondrial depolarization (Kitazawa et al., 2003). Therefore, chosen dieldrin as a model endocrine disrupting compound due to its accumulation in humans show both oestrogenic and antiandrogenic effect having the capability to amplify ER expression and stimulate a broad variety of intracellular mechanisms (Tabb and Blumberg (2006). One main difficulty with examination of endocrine disruption revolves about the dosage of chemicals to be employed.
A current study reported women adipose dieldrin concentrations 14 times greater than in their blood (1.21 p.p.b. (Botella et al., 2004), important maternal fat mobilization take place through the third trimester of pregnancy and lactation dieldrin concentrations in breast milk are approximately 50 p.p.b (Harris et al., 1999). The human fetus and neonate are potentially exposed to the milk are approximately 50 p.p.b (Harris et al., 1999). The human fetus and neonate are potentially exposed to the EDs through the second developmentally critical period of elevated testosterone approximately, 2 months postpartum. A complicate factor is discrepancy in exposure levels in non-adipose tissues and the quantity of endocrine disrupting compound transmission from mother to fetus (Cooke et al., 2001).

**DDT**

DDT, chlorodiphenyltrichloroethane was broadly used to control malaria in many countries in the planet. In the 1970s and 1980s many developed countries banned its use because of its extensive persistence in the environment which effect human health (Turusov et al., 2002; U.S. EPA, 1997; van Wendel et al., 2001). DDT is the major pesticide used for mosquito control. Mexico used DDT in malaria fight until 1999, due to low fee and lack of acute toxicity to expose populations (Schofield, 2001; Walker, 2000). Mexican vector control employees were subjected to soaring levels of DDT contact which found in adipose tissue throughout the anti-malaria (Rivero-Rodriguez et al., 1997). There are no information on paternal exposure to DDT and reproductive outcome such as spontaneous, alteration, congenital malformations, and abortion of the sex ratio, which are indicators of teratogenicity (Hauser et al., 2003; Martin et al., 2002).

A number of studies on DDT and some organic solvents reported reduce fertility, changed sperm counts and delay puberty (Santamarta, 2001; Jequier, 2002; Waisssmann, 2003; Metzler, 2002; Moreira and Wolff, 2003; Hakin and Oates, 1997). The estrogenic activity of DDT isomers is extremely weak as compare to estradiol but the properties of bioaccumulation and lengthy half-life point out that human contact levels can cause estrogenic (Santamarta, 2001; Gray Jr. and Kelce, 1996) and also cause androgenic agonist at high doses. DDE which is metabolite of DDT also have anti-androgenic action and have also the ability to jeopardize estrogen metabolism in its synthesis or breakdown and physiological elimination (Toppari, 1996; Kelce, 1995; Potashnik and Abeliovich, 1985).

**Zearalenone**

Zearalenone (ZEA, F-2 toxin) is a nonsteroidal oestrogenic mycotoxin created by a range of Fusarium fungi which are common contaminants of cereal crops worldwide (Zinedine et al., 2007). ZEA is found in maize or corns with the maximum concentration in wheat, bran, corn and their products. ZEA is mainly a field pollutant, conversely the toxin manufacture can also happen through storage in pitiable conditions (E.F.S.A, 2011). It has been also shown that ZEA is transported from the fields to the marine by rain water (Waskiewicz et al., 2012). The concentration in food stuff as well as in feed differs over a wide range which depends on climatic situations. The mean level of human daily intakes of ZEA is differ from 2.4 to 29 ng/kg b.w./day in adults while toddlers (12–36 months old) contain the maximum average every day intakes range from 9.3 to 100 ng/kg b.w./day (E.F.S.A, 2011). It has been shown that ZEA can also be excreted into cow milk (Prelusky et al., 1990). ZEA is quickly absorbed following oral administration. Its uptake is expected to be about 80–85%, but it is complex to evaluate owing to widespread biliary excretion. ZEA
and its derivative are identified in blood up to 30 min after oral administration bound to human globulins as reproductive hormones (Olsen et al., 1987; Biehl et al., 1993). Several studies with radio labelled zearalenone in rats confirm the distribution to estrogen target tissues for example uterus, interstitial cells of the testes and ovarian follicles. A few radiolabels were also identified in adipose tissues, indicative of the storage in adipose tissue may take place. The major effect of zearalenone results from its oestrogenic activity. ZEA and its derivative α-zearanenol (α-ZOL) and β-zearalenol(β-ZOL) compete with 17β estradiol (E2) for the definite binding site of oestrogen receptors (ERs). Several analyses have confirmed the binding of ZEA and its derivatives initiates oestrogen receptors (ERs). Several analyses have confirmed the binding of ZEA and its derivatives initiates series of events known to follow oestrogen stimulation (Kuiper-Goodman et al., 1987). Competence of binding of ZEA to ER in a target tissues is<1–10% than that of E2 whereas αZOL shows strong binding and βZOL lower affinity to ER (European Commission Opinion of the Scientific Committee on food on Fusarium Toxins, 2000). The specific manifestations of ZEA arereliant upon the species relative dosage and life stage throughout which ZEA is consumed. The most perceptible species is the pig, conversely it has been shown that ZEA can also have adverse effects on other species include rodents. It has been shown that ZEA and α-ZOL affect steroidogenesis in adult mouse Leyidig cells in vitro. During this study authors observed a decrease of testosterone production in cells co-treated with ZEA or α-ZOL and human chorionic gonadotropin (hCG). They also detected decreased expression of 3β-hydroxysteroid dehydrogenase/isomerase (3β-HSD-1), cytochrome P450 side chain cleavage enzyme (P450scc) and steroidogenic acute regulatory protein (StAR), which play a crucial role during steroidogenesis. In adult animals testosterone is critical for proper spermatogenesis and sperm maturation, and disruption of spermatogenesis can thus adversely affect male fertility. The negative effect of ZEA on reproductive parameters can also be observed in vivo Yang et al., 2007. Adult malemice were exposed to intraperitoneal injections of ZEA or α-ZOL at the concentration 0, 25, 50 or 75 mg/kg b.w. every day for 7 days. In all groups the authors observed significantly increased number of abnormal spermatozoa and significantly decreased number of live spermatozoa. Testicular and cauda-epidymal sperm counts were also reduced, as well as serum testosterone. These effects were observed in the treated males at all doses in a dose-dependent manner. Besides the decrease in sperm quality, a significantly low pregnancy rate was observed when untreated females were mated with the treated males. At high concentrations (50 and75 mg/kg b.w.), authors noticed a decrease of b.w. and increase of relative seminal vesicle weight (Kim et al., 2003). To show whether the action of ZEA includes induction of apoptosis of testicular cells, Kim et al exposed 10-week-old male mice to a single intra-peritoneal dose of ZEA (5 mg/kg b.w.) and analyze at 3.6, 12, 24, or 48 h after exposure. Germ cell degeneration caused by apoptosis was observed at stages I–VI of spermatogenesis 12 h after the exposure. The frequency of TUNEL-labeled germ cells increased in a stage-specific method with progressively increasing frequency at stages I–VI of seminiferous tubules with the time after exposure. These results show that a single dose of ZEA induces testicular germ cell apoptosis in a time-dependent and stage-specific manner in the rat testis in vivo. The induction of apoptosis in testicular tissue after ZEA treatment was also shown by Yuan et al. (2010).

CONCLUSION

Farmers in district Lower Dir are chronically exposed to various pesticides. These pesticides in men cause infertility, as observed in the Health Care Laboratory, Bakhella, Pakistan. In 620 infertile men, about 551 were directly or indirectly exposed to various pesticides (Unpublish data). These farmers are advised to minimize their contact with pesticides by using mask, gloves and other coverings. The farmers should be aware about the toxic effects of pesticides. The pesticides containers should be dispensed properly.

REFERENCES


Charkoudian N, Joyner MJ (2004). Physiologic considerations for...


Perspect 105, 308–314


Wastes. 25(1):87–103.


